ITEM No. 24
FILE No. XXIV—20

COPY No. 108

WORK ON ANTIMALARIALS
I.G. FARBENINDUSTRIE, ELBERFELD

COMBINED INTELLIGENCE OBJECTIVES
SUB-COMMITTEE

SECRET

AN EVALUATION OF THE WORK ON ANTIMALARIALS OF THE I. G. FARBENINDUSTRIE, ELBERFELD, GERMANY VISITED 30 MAY - 1 JUNE 1945

Reported By

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CIOS Target Number 24/3
Medical

COMBINED INTELLIGENCE OBJECTIVES SUB-COMMITTEE
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SECRET

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General Comments

The laboratories of I. G. Farbenindustrie, Elberfeld, were visited on 30 May and 1 June, where the undersigned interrogated Drs. Kikuth, Schönhöfer, Andersag, and Mauss relative to the nature and pharmacological properties of antimalarial drugs with which these investigators have been concerned.

Careful questioning, to which the Germans were willingly responsive, revealed the fact that practically all information of importance concerning these drugs had been given to Lt. Col. Hamilton Southworth, of CIOS Team 110, during his visit to Elberfeld. Fortunately, the writer, prior to his arrival in Germany, had the opportunity of examining this information which was brought to Paris by Lt. Col. Southworth on the afternoon of the day the writer arrived in Paris from London.

This comprised lists of those drugs whose activity has been assayed in humans, and of those drugs which had been prepared as potential antimalarials and assayed for activity in birds. The latter comprise five groups of compounds, viz, derivatives of acridine, of 8-aminoquinoline, of 4-amino-quinoline, of 3'-5'-dibromsulfanilanilid and 2,4-dialkyl-4-hydroxyquinoline. In the order given, these are termed by the Germans drugs of the Atebrine, Plasmochin, Sontochin, Bemural, and Endochin types.

In this connection it should be noted that the group of workers at Elberfeld who are concerned with the development of new antimalarial drugs, have, during the past decade, centered their attention upon the preparation of drugs of these five types. Other preparations made in the laboratory for various purposes by chemists not primarily concerned with potential antimalarial drugs, frequently find their way into the laboratory of Dr. Kikuth where they are subjected to an evaluation of antimalarial potency. Curiously enough, the investigators at Elberfeld have failed to find activity in the wide variety of chemical structures which have been reported in the United States to exhibit some degree of antimalarial activity when assayed in birds.

For example, a large number of sulfonamides, including such well known substances as sulfathiazole and sulfapyridine have been examined with completely negative findings. While this is of little practical importance, it does indicate that the screening methods in vogue at

Elberfeld are not as well adapted to detecting a low order of antimalarials potency as are the methods currently in use in the United States. This probably accounts for the failure of the German investigators to detect antimalarial activity in the wide variety of basic chemical structures in which such activity has been observed in the United States, and also accounts for the emphasis which they have placed upon investigations of the five series of compounds mentioned earlier in this report.

In this connection it may be well to point out that as a consequence of the writer's discussions with the group at Elberfeld it is his impression that while the chemists are exceptionally competent, the pharmacological examination of drugs is poor by American standards and the clinical evaluation of antimalarial drugs is carried out in an exceptionally poor manner. At present, and for the past few years, only two organic chemists have been employed full time on the synthesis of antimalarial drugs.

Screening Methods

At Elberfeld all assays of antimalarial potency are conducted in the laboratory of Dr. Walter Kikuth by means of canaries infected with either P. relictum or P-cathemerium. Infections of the birds with these parasites is achieved by blood inoculations or by the injection of sporozoites obtained from the salivary glands of infected mosquitoes. All drugs are administered in solution or suspension via stomach tube and but a single dose is given daily. As the details of these procedures have been described in the report of CIOS Team 110, they will not be detailed here.

In normal times when rice finches are available, experiments are also carried out with hemoproteus infections in order to evaluate the gametocidal activity of drugs.

From time to time Dr. Kikuth has worked with chicks infected with P. gallinaceum, but he insists that the degree of parasitization obtained in this infection is too variable to permit its use for evaluating the potency of potential antimalarial drugs. In discussion of this objection to the use of P. gallinaceum, Dr. Kikuth expressed the opinion that this variability might be offset in a statistical sense by the use of large numbers of chicks, but he pointed out that for the past few years it has been impossible to obtain chicks in large numbers

in Germany and that even if they had been obtainable, it would have been impossible to obtain an adequate supply of feed.

Furthermore, Dr. Kikuth is of the opinion that since a fair parallelism exists between the activity of known antimalarial drugs in canaries infected with P. relictum or P. cathemerium and the activity of these substances in humans, there is little point in exploring the potentialities of other avian parasites for the purpose of screening antimalarial drugs.

Clinical Examination of Drugs

When a new drug is encountered in Dr. Kikuth's laboratory, which exhibits a degree of antimalarial activity of sufficient magnitude to warrant examination in humans, it is turned over to the pharmacological laboratories of the I. G. Farben Werke where it receives a rather superficial examination.

Following the pharmacological examination of a new drug intended for clinical trial, it is sent to Prof. Sioli of Düsseldorf, who is supplied with the results of the screening and pharmacological examinations of the drug identified by a trivial name only. The chemical nature of the drug to be examined by Sioli is not disclosed to him.

According to Kikuth, Sioli frequently judges the effectiveness of a new antimalarial drug by purely clinical observations, such as the effect of the drug upon the course of the patient's fever, without an examination of the effect of the drug upon the course of the parasitemia. Indeed, Kikuth informed me that Sioli had assayed several of the I. G. preparations in humans infected with malaria before he had ever seen a parasitized erythrocyte.

In response to a question, Kikuth stated that he did not approve of Sioli's procedure in evaluating the potential usefulness of antimalarial drugs, but there was little that could be done about it since Sioli was a busy man. In other respects Sioli was cooperative and the proximity of his clinic to Elberfeld enabled the staff of the I. G. laboratories to keep in close touch with the progress of Sioli's investigations.

In the event Sioli finds a given drug to be inactive, little more appears to be done with it. If a drug exhibits some degree of activity according to Sioli, it is the

intention of Kikuth to have the drug examined elsewhere, particularly by Prof. Walter Menk of the Institut für Schiffs-und Tropenkrankheiten in Hamburg. The services of Menk have not been available recently because of his service with the German army in the field. In the future, it is the intention of Kikuth to have all clinical trials of new drugs or combinations of drugs made by Menk rather than by Sioli.

The Relapse Problem

Dr. Kikuth was questioned on the nature of any experiments that he or his associates had made upon the problem of relapses in P. vivax infections. He replied that he had long realized this was a major problem in the therapy of malaria, that he had repeatedly pointed out in his writings that relapses were probably due to the persistence of exoerythrocytic forms of the parasite which are not affected by the conventional antimalarial drugs and that he had long tried to interest Sioli in conducting some experiments upon the treatment of relapses, but had been unable to interest his clinical colleague in such experiments.

Kikuth stated that he had been called into consultation by the High Command of the German army who hoped that he would be able to suggest some method of preventing relapses following an initial attack of malaria. In this connection, Kikuth volunteered the information that German soldiers who acquired P. vivax infections while fighting on the Russian front, suffered relapses to such an extent that their illness accounted for the loss of the services of two divisions for 208 days. He stated that these figures were given to him by representatives of the German army who consulted him.

Kikuth was unable to furnish any further figures concerning the incidence of relapses in the German Army as a result of primary infections acquired on the fronts. However, he did remark upon the fact that when German Troops, who had little trouble with malaria in Italy owing to the use of quinacrine as a suppressive agent, were transferred in the fall to non-malarious regions, they commonly experienced a primary attack of the disease in the spring several months after the cessation of the use of quinacrine.

Kikuth has prepared a manuscript for publication upon the problem of relapse in benign tertian malaria. A careful reading of the manuscript disclosed that it is

merely a review of the literature which has been for the most part more extensively reviewed on pages 63 to 76 of Kikuth and Menk's "Die Chemotherapie der Malaria" 2. Auflage.

In the manuscript referred to, Kikuth lays considerable emphasis upon the use of a combination of quinine and plasmochin in the therapy of P. vivax malaria as a means of lowering the relapse rate. This, of course, was claimed by Sinton and Bird some seventeen years ago, by Jarvis (1932) and by several other authors. It is the writer's understanding that Kikuth's attention was drawn to this mode of treatment by a reading of "Malaria in the Netherlands" by N. H. Swellengrebel and A. de Buck, Amsterdam 1938, wherein (pages 188-190) the experiments of Piebenga are cited. This investigator was a physician at a mental hospital at Franeker in the Province of Friesland, where a large number of the inmates suffered from naturally-induced malaria which is common in the region. Piebenga began his experiments in 1934 and they were continued thru 1937 by Dr. van Andel.

These investigators found that when 119 of their patients were treated for a fortnight with daily doses of 14 grains of quinine and 1/2 grain of plasmochin 30 patients (25%) suffered relapse within the two year period following the course of treatment. When the same regimen of therapy was followed for three weeks in a group of 115 patients, 2 relapsed during the year following treatment and 8 others suffered relapses during the second year, following the period of treatment. In his manuscript and in conversation, Kikuth emphasizes the relapse rate of but 2% and neglects the fact that the investigators who conducted this experiment cite a relapse rate of 10%. When questioned on this point Kikuth stated that there is no assurance that the 8 patients who relapsed in the second year following treatment were not reinfected by natural means.

In their discussion of these experiments Swellengrebel and de Buck (loc. cit.) remark that these experiments made at Franeker were brought to an end as a consequence of gastric complaints which occurred frequently during the third week of treatment with quinine and plasmochin. The Dutch authors believe it "unsafe to recommend the 3 weeks course of treatment in general practice." Despite this, Kikuth recommended that such a course of treatment be used by the German Army. According to Kikuth, this mode of

therapy was never put into practice during the war because of the non-availability of quinine.

As a substitute it was recommended that treatment with quinacrine and plasmochin be adopted instead. This was done but proved unsuccessful because of the high incidence of toxic reactions. The outstanding symptom of these was intense abdominal cramps. According to Dr. Schönhöfer with whom I discussed this, appendectomies were performed upon a number of German soldiers because of these cramps induced by a combination of quinacrine and plasmochin. This is an interesting commentary on the diagnostic skill of German physicians.

Kikuth and Schönhöfer both believe that the toxicity of quinacrine and plasmochin are additive and that quinine actually lowers the toxicity of plasmochin. When questioned upon this, these individuals referred the writer to Dr. Hecht, a pharmacologist, for further information. Dr. Hecht stated that the toxicity of plasmochin and quinacrine appeared to be additive when the toxicity was measured in terms of the doses necessary to cause death in various species of laboratory animals. He had performed no experiments himself upon the influence of quinine upon the toxicity of plasmochin but referred to the experiments of Fritz Eichholtz, formerly of the I. G. laboratories and now professor of pharmacology at Heidelberg. According to Eichholtz, plasmochin produces a cardiac arrythmia and fall in the blood pressure of cats which does not occur if quinine is also administered. (See Beihefte zum Archiv für Schiffs- und Tropen- Hygiene, Pathologie und Therapie Exotischer Krankheiten, 1927)

The I. G. laboratories manufacture a product known as Atepe Tablets each of which contain 100 mg. quinacrine and 5 mg. of plasmochin. According to Kikuth these were used by Franco's army in Spain during the Spanish Revolution for the treatment of malaria with good results. When questioned on the nature of these "good" results, it developed that no information was available, but that the results were assumed to be good since no complaints were received and additional sales were made. Because of this and because of the aforementioned lack of quinine in Germany, Atepe tablets were recommended for use in the German Army who were advised to treat malaria cases by administering 300 mg. of quinacrine daily for 5 to 7 days and then Atepe tablets b.i.d. for 3 days. This proved to be the maximum quantity of plasmochin that could be administered without the onset of the abdominal cramps mentioned earlier. No

data on the results of this treatment were available at Elberfeld although both Drs. Kikuth and Schönhöfer, interviewed separately, agreed that the treatment was unsuccessful in its objective of lowering the relapse rate by any marked degree.

As will be noted later, Certuna, a structural analogue of plasmochin, is claimed to be less toxic than is plasmochin. When asked if Certuna had been tried in combination with quinacrine as a means of lowering the relapse rate, Kikuth replied that it had not, and that he would not recommend such a trial, because unlike plasmochin, Certuna is without action upon the E.E. forms of the malaria parasite.

Both Drs. Schönhöfer and Andersag agreed that the problem of relapse in malaria will not be solved until some entirely new type of drug is forthcoming. It is their belief that there is little point in exploring the further potentialities of drugs of the plasmochin and quinacrine series for this purpose. These chemists, and Kikuth as well, believe that a useful drug may be encountered in the Endochin series which will be discussed presently.

Causal Prophylaxis

The investigators at Elberfeld all realize the desirability of finding a drug which will be a true causal prophylactic. Up to the present only one drug has been found which behaves as such in avian infections. This substance is Endochin. Kikuth has found that a single dose of 40 milligrams of this substance per 20 gram canary administered 1 hour after the injection of sporozoites of either P. relictum or P. cathemerium, confers complete protection from infection upon the birds. The prophylactic activity of this substance against P. vivax in humans was examined by Sioli in two patients with negative results. As this drug also proved to be inactive in blood induced P. vivax malaria, Schönhöfer and Kikuth believe that it may not have been absorbed by the patients. No experiments were carried out in humans to test this hypothesis.

Cure of Avian Infections

In reply to a question on this topic Kikuth stated that he had never been able to obtain a permanent cure of infected canaries with any drug.

Synthetic Antimalarial Drugs

Since 1939 the chemical department of the I. G.

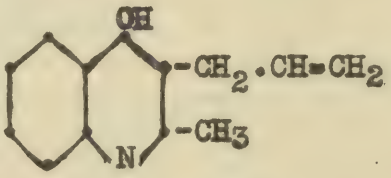
laboratories has prepared for examination 18 acridine derivatives (Quinacrine series), 24 derivatives of 8-aminoquinoline (Plasmochin series), 45 derivatives of 4-aminoquinoline (Sontochin series), and 132 derivatives of 2,3- dialkyl-4-quinolol (Endochin series).

From these figures it is evident that in recent years emphasis has been placed upon the last named group of substances.

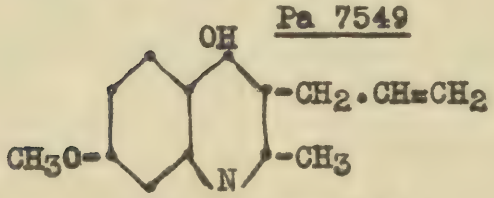
The Endochin Series

The first number of this series found to exhibit antimalarial activity in canaries was 2-methyl-3-allyl-4-hydroxy quinoline (PA 7549) which was prepared under the direction of Dr. Andersag as an intermediate for the preparation of the corresponding analogue in the 4-aminoquinoline series. This substance was found to be active when administered to canaries in doses of 0.7 mg per 20 gm in the Roehl test. The introduction of a methoxy group into position 6 of this substance was found to abolish activity, while the substitution of such a group in position 7 to form Pa 7776 was found to enhance activity and endow the parent structure with a trace of activity against sporozoites.

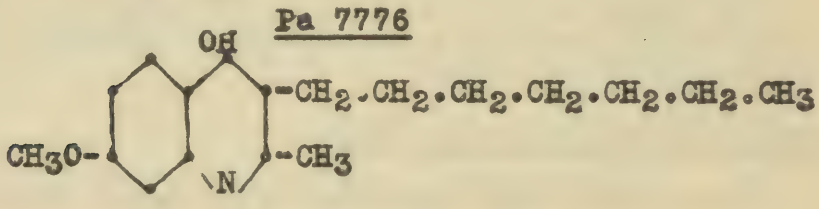
This observation led to the preparation of an extended series of structural analogues of these substances by Andersag and Salzer which culminated in the preparation of Endochin (Pa 8343) by Salzer in 1940. As has been mentioned earlier in this



Pa 7549



Pa 7776



report, this substance has been found to be a causal prophylactic in canaries and to effect clinical cures in such birds when administered in doses of 1.2 mg. per 20 gm. for 5 days. This substance was found to prevent the development of infection in birds inoculated with sporozoites in doses of 5 mg. per day for 5 days and exhibited gametocidal action in doses of 0.15 to 0.3 mg. per 20 gm. per day.

Kikuth believes that Endochin may have an action upon the EE forms of the malarial parasite but he has no direct experimental evidence bearing upon this point. Because of this belief, Kikuth expects that a drug which will be effective in the prevention of relapses may ultimately be found among the congeners of Endochin. The chemists Schönhöfer and Andersag are less hopeful of success in this field because they feel that in the preparation of the 132 members of the Endochin series of drugs they have practically exhausted the possibilities of substitution in the Endochin molecule.

The nature of the various derivatives of Endochin which have been prepared in the I. G. laboratories will not be considered here because a list of all of these has been obtained by Lt. Col. Southworth of CIOS Team 110.

Endochin was prepared at the I. G. laboratories from m-anisidine and ethyl n-heptylacetoacetate by means of a conventional Conrad-Limpach reaction. The details of this preparation have been obtained by Dr. Kleiderer of the CIOS Team which he led. Numerous congeners of Endochin were prepared in the same manner by the interaction of various aromatic amines with appropriately substituted acetoacetic esters. Some derivatives of Endochin were prepared by replacement of the hydroxy group in position 4 with chlorine and subsequent interaction of the halogenated quinoline with various amines, thiols, etc. In general, all such substitutions were found to cause a marked diminution in antimalarial activity. Indeed, most of the 4-substituted Endochin so prepared were found to be inactive when assayed in Kikuth's laboratory.

In passing, it is of interest to note that the activity of Endochin appears to depend in part upon the presence of a methyl group in position 2 of the quinoline nucleus. The analogue of Endochin which does not contain this group was found to have an activity of less than 1/20 that of the parent drug.

Pharmacology of Endochin

The toxicology of Endochin was examined by Dr. Hecht

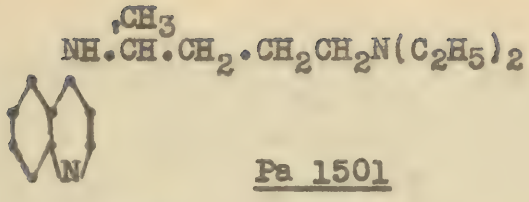
prior to the submission of this drug to Prof. Sioli for clinical evaluation. The drug was administered per os to cats and rabbits in doses of 50 to 200 mg/kg daily for 6 days without any evidence of toxicity. Two rabbits were given 100 mg/kg of the drug per os for 15 days. The urine of one of these animals became turbid but no albumin was excreted. No other symptoms of toxicity were observed. Of two cats that received 100 mg/kg of Endochin daily, one suffered a marked weight loss and died on the 10th day. At autopsy, evidence of pericarditis, probably unrelated to the intake of drugs, was observed. The other cat received the stated dose of the drug for 15 days without weight loss or other evidence of toxicity.

Intraperitoneal injection of the drug into rats in doses of 100 to 500 mg/kg sometimes caused death. In rats that survived the latter dose, unabsorbed drug was found in the peritoneal cavity 8 days after its administration.

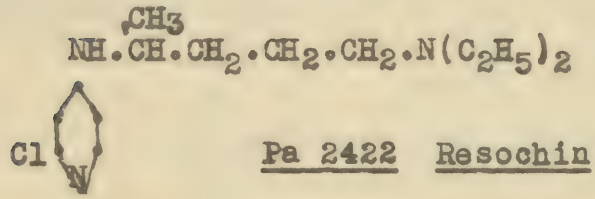
The intravenous toxicity of Endochin was determined by the injection of solutions of the drug in N-methylacetamide. A dose of 10 to 40 mg/kg of the drug so administered elicited no symptoms other than the narcotic effect due to the solvent used. A dose of 60 mg/kg of Endochin injected intravenously into rabbits caused their death. In similar experiments with cats, a dose of 20 mg/kg caused ataxia and doses of 30-40 mg/kg caused death by respiratory paralysis. In these experiments, all injections were made "fairly rapidly".

4-Aminoquinolines

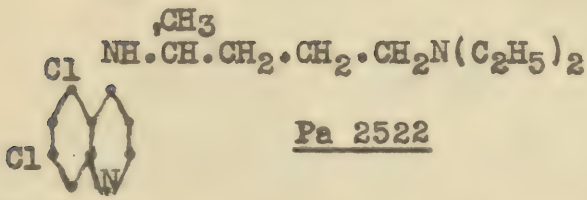
In the period from 1929 to 1943, 172 derivatives of 4-aminoquinoline were prepared in the I. G. laboratories. Up to 1934, 14 members of this series were prepared and assayed for anti-malarial activity with negative results. The first member of the 4-aminoquinoline series to exhibit anti-malarial activity was Pa 1501 prepared by Pöhls at Leverkusen. This observation was the stimulus for the further exploration of the potentialities of the 4-aminoquinolines. As a result of examining the effect of nuclear substituents such as methyl, methoxy, halogen, phenyl, and benzyl groups upon the activity of drugs having the same basic structure as Pa 1501, Andersag and his collaborators in 1935 prepared the drug Resochin (Pa 2422) which was found to be about 30 times as potent as Pa 1501 when assayed by Roehl's method. Both Resochin



Pa 1501



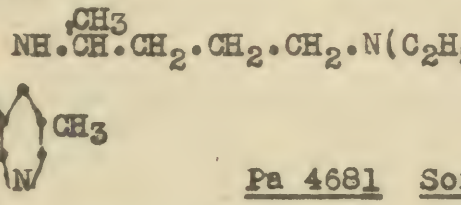
Pa 2422 Resochin



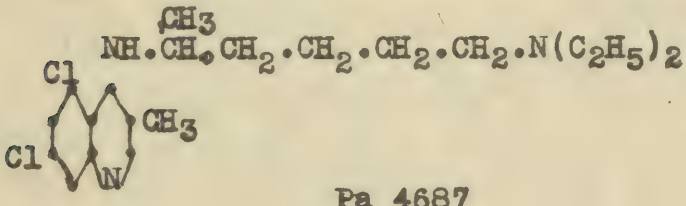
Pa 2522

and its 5 chloro derivatives (Pa 2522) were found active in canaries in doses of 1/3 mg/20 gm/day, and inactive at one half of this dose. The bromine and iodine analogues of Resochin were likewise prepared and assayed, but the potencies of these derivatives were found to be less than that of Resochin.

Two other derivatives of 4-aminoquinoline, Pa 4681 (Sontochin) and Pa 4687 were found active in doses of 2/3 mg/20 gm/day.



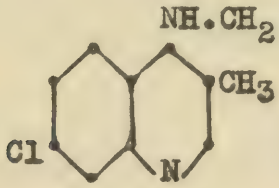
Pa 4681 Sontochin



Pa 4687

by Roehl's test.

A few analogues of Sontochin were prepared in which the methyl group in position-3 was replaced by other groups such as n-butyl, phenyl and 4'-chlorophenyl. As such substitutions uniformly led to a decrement in activity, analagous compounds were not explored. A number of variations were also made in the side chain of Sontochin without any enhancement in activity. But one of these, Pa 7621 (Brachysan), need be considered here.



Pa 7621 Brachysan

Of the many 4-aminoquinoline derivatives prepared in the I. G. laboratories, only three have been tested in humans with blood induced infections of P. vivax. Resochin was tested by Sioli who believed it to be too toxic for practical use and abandoned this drug in favor of Sontochin. According to Kikuth, Sioli (1938-39) found the latter drug to be as active as quinacrine in humans. Clinical cures of blood-induced B.T. malaria were obtained following the administration of 0.1 gram of Sontochin t.i.d. for 5 to 7 days. No evidence of toxicity were observed when three times this does was given to patients for a like period of time.

These experiments were subsequently confirmed by Prof. Mühlens of Hamburg.

Despite these results, Sontochin was never brought into production at Elberfeld. Drs. Hörlein and Schönhöfer stated that only 20 to 30 kg. of this drug had been manufactured and that they entertained doubts as to the feasability of preparing it upon a large scale because of synthetic difficulties. When questioned further upon this, they agreed that these difficulties could probably be surmounted if it should become necessary, but, they added, it was their belief that the cost of production would render the drug too expensive to compete with quinacrine, over which it possesses no advantage, other than the fact that it is colorless.

Brachysan, Pa 7621, prepared in 1943 by Andersag and Breitner, was tested clinically by Sioli in 1944 who obtained cures of blood induced vivax malaria by the administration of 0.1 gram t.i.d. for 7 days. Sioli noted that doses of 0.3-0.5 gram of this drug on two successive days brought about the cessation of fever and parasitemia. The protocols of these experiments were obtained by Lt. Col. Southworth of CIOS Team 110.

Evidently the German Army became interested in Brachysan because Kikuth stated that Rose of the Luftwaffe had also tested this drug and found it necessary to employ a somewhat higher dose to obtain the effects achieved with a given dose of quinacrine. Drs. Andersag and Schönhöfer are of the opinion that this is of little moment, because Brachysan can be produced more cheaply than Sontochin. In consequence they believe that if a drug of the 4-aminoquinoline series is to be brought into general use, it will be Brachysan rather than the more expensive Sontochin.

Prior to 1939, Andersag and his assistants prepared a number of analogues of Sontochin from benzo-f-quinoline and benzo-h-quinoline. Further investigation of this series was abandoned because of the negligible anti-malarial activity of the substances prepared. Andersag hopes to continue his investigations of the 4-amino-quinolines by further explorations of the effect of modifications in the side chain of Sontochin.

So far as the writer could determine, the chemical staff of the I. G. laboratories have given little or no thought to the possibility of making similar modifications in the side chain of Resochin. It appears to be their belief that the lack of a methyl group in position-3 of the quinoline nucleus is responsible for the toxicity of Resochin which Sioli is said to have observed.

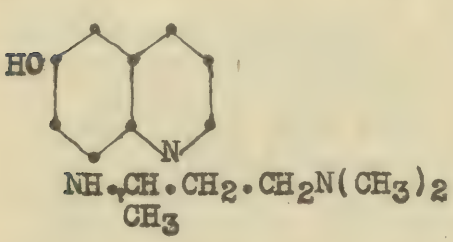
Although the supposed toxicity of Resochin was mentioned several times during the writer's conversations with the staff of the I. G. laboratories, no protocols of Sioli's observations on humans who received this drug were available. According to Kikuth, such were never submitted by Sioli, who merely informed Kikuth verbally that the drug (Resochin) was too toxic for practical use in humans and that he therefore proposed to concentrate his efforts upon the clinical evaluation of Sontochin which he received for examination at approximately the same time.

Derivatives of 8-Aminoquinoline

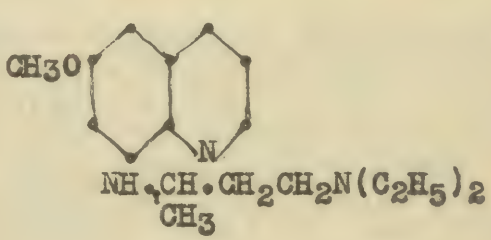
A large number of these derivatives have been prepared in the I. G. laboratories. In general, these fall into two classes; derivatives of 8-amino-6-hydroxy-quinoline and derivatives of 8-amino-6-methoxy-quinoline. The former constitute the Certuna series of drugs and the latter the Plasmochin series.

Kikuth and Schönhöfer believe Certuna to be the most promising member of the derivatives of 8-amino-6-hydroxy-quinoline prepared in the I. G. laboratories. Certuna, formerly called Cilional and Oprochin, was developed some years ago in the I. G. laboratories. According to Kikuth this substance is less toxic than plasmochin in humans and has a gametocidal activity of about the same order as that of plasmochin. This was shown by Sioli, Mühlens, and Missiroli in 1938. Kikuth believes that, unlike plasmochin, Certuna is without effect upon the E.F forms of avian parasites. While he has no direct evidence for this statement, he infers this from the fact that in sporozoite-inoculated canaries, Certuna causes no delay in the appearance of trophozoites while Plasmochin does. In consequence, Kikuth is emphatic in his belief that Certuna would be useless as a means of preventing relapses if used in combination with quinine or other trophozoiticidal agents.

Kikuth stated that Certuna was prepared and used in Italy but had never been marketed by the I. G., because the sales department of that organization felt that they were not in a position to market substances primarily of interest as gametocidal agents. In this connection, Kikuth added that the field of application for such agents was decidedly limited and that it was his opinion that they are of practical use only in a restricted area such as that of a plantation.



Certuna

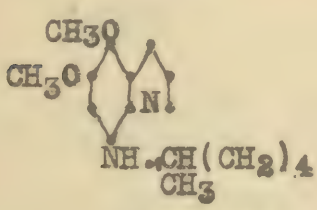


Plasmochin

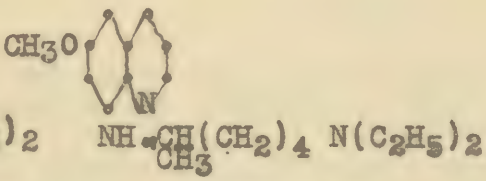
The Plasmochin Series

Dr. Schönhöfer was questioned about developments in the Plasmochin series. Since 1929 some 220 odd analogues and derivatives of Plasmochin have been prepared in the I. G. laboratories. In general, all of these have been found to be less potent than Plasmochin when assayed in canaries, hence they have not been submitted for clinical trial.

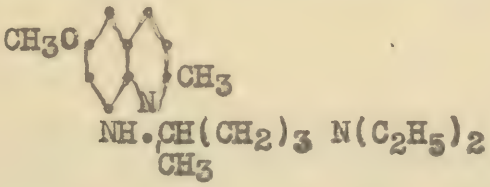
Of the many Plasmochin derivatives prepared since 1924 only fourteen have been subjected to clinical trial in man. Three of these substances, Haprochin, Japrochin, and Andrachin, were found to be approximately six times as active as Plasmochin by Roehl's test, but all three were found to be no more active than Plasmochin when assayed in humans. Consequently no effort has been made to place these compounds in production.



Haprochin



Japrochin



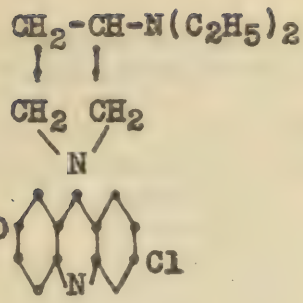
Andrachin

In response to a question, Schönhöfer stated that he had no immediate plans for the further investigation of drugs derived from 8-aminoquinoline. He hoped that some day he may be able to couple Plasmochin with another molecule in a fashion such that the conjugate would be less toxic than the parent drug and would be slowly degraded in the body to Plasmochin. This concept is akin to that employed in the preparation of substances of low toxicity by the union of diamino diphenyl sulfones, etc., with sugars.

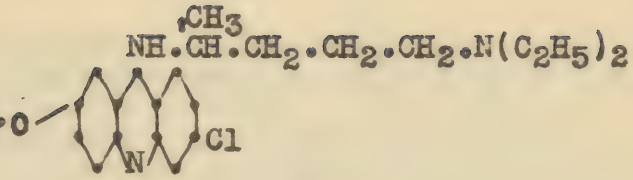
Acridines

In the years between 1929 and 1942, 300 odd derivatives

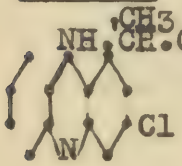
of acridine structurally related to quinacrine, were prepared in the I. G. laboratories. Assays of these substances by Roehl's method disclosed that the majority of them were either inactive or of such a low order of activity as to be of no interest. A few of these substances (Pa 8861, Pa 3721, Pa 938, and P 6956) were found to be as potent as quinacrine but were not further investigated because of their lower chemotherapeutic indices in canaries.



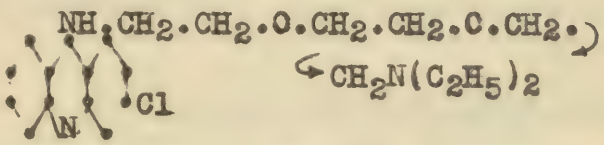
Pa 8861



Pa 3721



P 6956



Pa 938

Because of this none of these substances were submitted for pharmacological examination or clinical testings.

No new members of the acridine series of antimalarial drugs have been made since 1942, and no further work in this field is contemplated at the present time in the I. G. laboratories.

Sulfonamides

Mietzsch, who was one of the inventors of quinacrine, has been working on the synthesis of sulfonamides for the past decade and with his associates has produced a large number of such compounds. Kikuth has tested a great many of these for antimalarial activity against P. relictum and P. cathemerium with negative results.

One substance, Bemural (3',5'-dibromsulfanilanilid) was found to be about 1/2 as active as quinacrine when assayed by Roehl's method and to exhibit some activity against sporozoites. Thirty-six derivatives and analogues of Bemural were prepared and assayed for activity. All of these proved to be less active than Bemural.

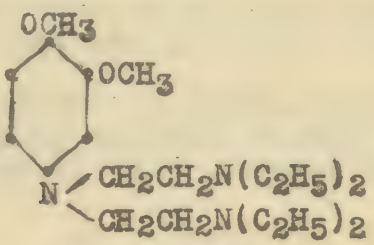
Kikuth believes that Bemural might prove to be a causal prophylactic in man, but he has no information on this matter. According to Kikuth, a quantity of Bemural

was sent to Hamburg for clinical trial but no report upon its activity in man has yet been received in Elberfeld.

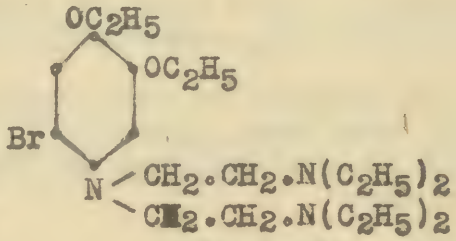
In this connection, it should be noted that Comdr. Charles L. McCarthy has reported under date of 29 May 1945, that a clinical evaluation of Bemural was undertaken in the Pfafferode Heilanstalt für Geisteskrankheiten in Mühlausen. According to the information obtained by Comdr. McCarthy, the investigators working under the direction of Dr. Blaurock in this institution have tried Bemural in a dose of "4 tablets" a day for 6 days in 30 to 40 patients without definitive results. For some reason not clearly stated in the Commander's report, Blaurock believes Bemural may have some value as a prophylactic agent.

Dimeplasmin and Diapromin

The structure of these two substances are shown below. Their preparation is



Dimeplasmin



Diapromin

described in German Patent 499,826 issued 23 June 1930. Kikuth states that Dimeplasmin is about 1/16 as potent as Plasmochin when assayed by Roehl's method but that it is a more potent gametocidal agent. Since Kikuth believes that drugs which are gametocidal will also be active against EE forms, he recommends that Dimeplasmin be given a trial as a means of preventing relapses. For this purpose, Dimeplasmin should be used in conjunction with some antitrophozoite agent such as quinine or Plasmochin. According to Kikuth, such an experiment has not been conducted in Germany.

Dimeplasmin was tested against blood induced vivax malaria in 1928 by Sioli who administered 0.8 to 2.0 grams per day to his patients for 6 days without perceptible effect upon the course of the infection. The prophylactic activity of Dimeplasmin has not been adequately explored.

The chemists working under the general direction of

Schönhöfer have prepared a number of derivatives and analogues of Dimeplasmin. None of these have been found to be more potent than the parent Dimeplasmin. Accordingly, Schönhöfer considers it improbable that any highly active compound will be found by further explorations of compounds of this type.

Kikuth stated that Diapromin had been examined by Sioli in 1936 in humans and that he had found this substance inactive both prophylactically and curatively.

Conclusions

A rather hurried and probably superficial examination of Kikuth's records convinced the writer that the German investigators at Elberfeld have not discovered by accident or by design certain types of compounds which have been found by investigators in the United States or England to exhibit antimalarial activity. This opinion was confirmed by questioning of Schönhöfer relative to the antimalarial activity exhibited by various types of chemical structures.

As in the United States, the Germans have assayed the antimalarial activity of numerous substances prepared for other purposes, i.e., dyes, insecticides, anaesthetics, etc., but they have failed to note the large variety of chemical structures which exhibit some degree of antimalarial activity.

It should be noted that all members of the staff of the I. G. laboratories seemed reasonably cooperative. So far as the writer could discern they made no attempt to conceal information. It is the writer's opinion that the staff of the I. G. laboratories do not have any leads or suggestions for new antimalarial drugs that might be of potential value in the United States as a guide for chemists working in this field.

No work has been carried on in the laboratories at Elberfeld for approximately two months. Kikuth comes to his laboratory irregularly in order to carry on the cultures of various types of parasites with which he has been working. He says that at present it is impossible to carry on active experimental work because of undernourishment of himself and of his staff, because of the time required to maintain a garden to supplement the present rations, and because of the difficulty in obtaining laboratory assistants, who see little point in working when their income is essentially useless as far as the purchase of food is concerned.